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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,698	02/10/2000	ODILE LEROY	99849-A	7060

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MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/423,698	LEROY, ODILE	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-27-07 has been entered.

Claims 1-31 are pending and under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chu et al (Infection and Immunity, 40(1):245-256, April 1983) in view of Merck and Co. Inc. (EP 0497 525, May 8, 1992) is maintained for reasons made of record and herein.

Applicants' arguments have been fully considered but are still not persuasive. Applicants argue that the results are not predictable. This is not persuasive, the results are demonstrably predictable and the art is replete with conjugated polysaccharides as immunogens and the skill in this art is very high. The art teaches all the *S. pneumoniae* polysaccharides and effective conjugate combinations were known. The art teaches the desirability for conjugation. The art demonstrates well before Applicants filing date that conjugate leads to increased immune response in the elderly and infants. Applicants merely selected among the known and desired options to form a new composition. Applicants focus on the TSM test and that it can be important to identify a reason. First, the record does identify a reason and the skilled artisan merely selected from a known combination of elements. The individual elements are expected to be immunogenic as have a plethora of polysaccharide conjugates in the art. The combination of the 23-valent vaccine is immunogenic; the combination of 23 different conjugates would be expected to be immunogenic as well. Applicants argue that Chu et al teaches away because it does not teach that the combination of the conjugates is better. This is not a teaching away because the proper basis for comparison is the unconjugated polysaccharide. The combination was to conjugate the unconjugated polysaccharide. Chu et al merely teaches that a single conjugate was able to maximize the immune response and that a further increase in dose was insufficient to further boost the immune response. All that this would have revealed to the skilled artisan is that one conjugate was sufficient to induce the maximal response to the same polysaccharide. This is not a teaching away. Applicants argue that the combination provided for increased immunogenicity at page 12 of the response as indicated in Chu et al is irrelevant because the claims are not so drawn. Applicants argue Merck separately and state that Merck only exemplifies single

conjugates and not combined conjugates. This is not a fair reading of Merck because Merck's base vaccine is 23 valent and Merck and Co. Inc. teach that since unconjugated polysaccharides are poor inducers of T-cell immune responses, conversion of the Pn-Ps into immunogens capable of inducing T-cell responses is the key to producing adequate protection in this target population. (see page 2, second full paragraph). One of skill in the art would have clearly read this passage as direction to derivatize the 23 valent vaccine by conjugating to the polysaccharides the proteins that should behave as an immune enhancer and that such immune enhancers are the outer membrane protein complex (OMPC) derived from *Neisseria miningitidis*, tetanus toxin, diphtheria toxin or pertussinogen may be used (page 3, lines 14-19 and page 16, lines 54-59). Therefore, the instant invention only combines prior art elements to yield predictably results. The desirability of conjugates were known, the capsular polysaccharides were known and the carrier proteins were known. The instant invention is a mere combination of known element having the expected property of immunogenic. This is application of a known technique to provide for predictable improvement of the 23 valent unconjugated vaccines. Furthermore, the combination is obvious to try under the argued "KSR standard" because Applicants merely selected for choosing a finite number of predictable solutions and the art known and demonstrated success with other polysaccharide conjugates in the field. The substitution of one carrier protein is obvious and provides for predictable results wherein the polysaccharide is still immunogenic. Applicants argue that one would not combine antigen unless there is a reasonable expectation of achieving a beneficial effect. This is again not persuasive because the 23 valent naked vaccine is currently on sale and provides for a beneficial effect. The conjugation merely provides for stronger responses. The combination of the different vaccines is given to children and the HiB conjugate is currently on sale for vaccination of children. There is no hesitation of giving multiple vaccines to infants in the medical arts. Applicants again argue the phenomenon of antigenic competition and that an immunologist would not combine due to this phenomenon.

This is again not persuasive, the 23 valent naked polysaccharide vaccine, in the field of immunology and medicine, is effective. Applicants' argument with respect to antigenic competition for the conjugates is a red herring because the 23 valent combination has been successfully used. This is not persuasive, antigenic competition does not prevent the 23 valent polysaccharide vaccine from being effective. Therefore, it logically follows that the 23 valent polysaccharide conjugate vaccine would be similarly effective. So while there may be some antigenic competition under some conditions with some antigens it does not make the combination of native 23 valent polysaccharide vaccine or it's conjugate ineffective for the intended use. Applicants argue that neither Chu et al nor Merck teach any advantages from altering their compositions per se. This flies in the face of the teaching of Merck. Merck may specifically reduce to practice a single conjugate, but Merck clearly recognizes that all the 23 valent polysaccharides can be conjugated and specifically contemplates diphtheria and tetanus toxoid. A reference is valuable for all it teaches, not just the claims. Applicants repeatedly argue the references individually and this is not persuasive because arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue in pages 13-14 that the Office has provided no reason to combine. This is simply not so and motivation has been provided in the previous rejection and further KSR analysis is provided herein and reiterated below.

"Merck's base vaccine is 23 valent and Merck and Co. Inc. teach that since unconjugated polysaccharides are poor inducers of T-cell immune responses, conversion of the Pn-Ps into immunogens capable of inducing T-cell responses is the key to producing adequate protection in this target population. (see page 2, second full paragraph). One of skill in the art would have clearly read this passage as direction to derivatize the 23 valent vaccine by conjugating to the polysaccharides the proteins that should behave as an immune enhancer and that such immune enhancers are the outer membrane protein complex (OMPC) derived from *Neisseria miningitidis*, tetanus toxin, diphtheria toxin or pertussinogen may be used (page 3, lines 14-19 and page 16, lines 54-59). Therefore, the instant invention only combines prior art elements to yield predictable results. The desirability of conjugates were known, the capsular polysaccharides were known and the carrier proteins were

known. The instant invention is a mere combination of known element having the expected property of immunogenic. This is application of a known technique to provide for predictable improvement of the 23 valent unconjugated vaccines. Furthermore, the combination is obvious to try under the argued "KSR standard" because Applicants merely selected for choosing a finite number of predictable solutions and the art known and demonstrated success with other polysaccharide conjugates in the field. The substitution of one carrier protein is obvious and provides for predictable results wherein the polysaccharide is still immunogenic."

The rejection is maintained.

New Rejections

Claims 1, 2, 4, 6, 7 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahman et al (Pediatr. Infect. Dis. J. 15:134-9, 1996) in view of Anderson et al (J. Pediatr. 128:649-53, 1996).

Ahman et al teach a pentavalent pneumococcal oligosaccharide conjugate vaccine PncCRM comprising oligosaccharides derived from capsular polysaccharides types 6B, 14, 18C, 19F and 23F conjugated to the nontoxic mutant diphtheria toxin CRM197 (see abstract and page 135, column 1, vaccines. The combined vaccine was able to induce an immune response in infants.

Anderson et al teach immunogenicity of a heptavalent pneumococcal conjugate vaccine in infants. The vaccine was a seven-valent (6B, 14, 19F, 23F, 18C, 4 and 9V) pneumococcal vaccine conjugated to the outer membrane protein complex of Neisseria meningitides (see abstract and page 650, columns 1-2 see vaccines).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to combine the two compositions together in order to form a third composition for the same use. Moreover, the courts have held in *In re Kirkhoven* (205 USPQ 1069, CCPA 1980) that "It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form third composition that is to be used for the very same purpose:idea of combining them flows logically from their having been individually taught in the prior art."

Claims 1-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahman et al (Pediatr. Infect. Dis. J. 15:134-9, 1996) in view of Anderson et al (J. Pediatr. 128:649-53, 1996) as applied to claims 1, 2, 4, 6, 7 and 14 supra and further in view of Merck and Co. Inc. (EP 0497 525, May 8, 1992).

The combination differs by not providing all conjugates differ or all conjugated to diphtheria toxoid or tetanus toxoid.

Merck and Co. Inc. teach conjugates of partially hydrolyzed, highly purified, capsular polysaccharide (Ps) from *Streptococcus pneumoniae* serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11 a, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F conjugated to a protein moiety (PRO) wherein the PRO that should behave as an immune enhancer and that such immune enhancers are the outer membrane protein complex (OMPC) derived from *Neisseria miningitidis*, tetanus toxin, diphtheria toxin or pertussinogen may be used (page 3, lines 14-19 and page 16, lines 54-59). Merck and Co. Inc, teach vaccines comprising a mixture from one to ten different pneumococcal polysaccharide-immunogenic protein conjugates (Pn-Ps-PRO) induce broadly protective recipient immune responses against cognate pathogens (see abstract; paragraph bridging pages 2-3 and page 50, claim 10). Merck and Co. Inc. indicate that a polyvalent vaccine comprising 23 unconjugated *Streptococcus pneumoniae* (Pn) polysaccharides is commercially available as "PNEUMOVAX^{TM}23" and accounts for 90 percent of pneumococcal blood isolates. Merck and Co. Inc, teach that the unconjugated vaccines are least effective in the elderly and infants under two years of age, and this is the segment of the population most at risk for pneumococcal infections. Merck and Co. Inc. teach that since unconjugated polysaccharides are poor inducers of T-cell immune responses, conversion of the Pn-Ps into immunogens capable of inducing T-cell responses is the key to producing adequate protection in this target population. (see page 2, second full paragraph).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to conjugate each *S. pneumoniae* capsular polysaccharide of Merck and Co. to different carrier proteins as taught by the art or any combination thereof because Merck and Co. teach that conversion of the naked capsular polysaccharide provides for better immunization in the elderly and infants and Merck et al teach suitable carrier proteins and the instant combination is merely a selection of known alternatives made by known art methods achieving a predictable result of producing a composition of PsPn polysaccharide conjugates that are immunogenic.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Lee et al (Vaccine 13(16):1533-1538, 1995) is cited to teach that immunogenicity of the 23-valent pneumococcal polysaccharide (unconjugated) vaccine in children.

Status of the Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor Shanon Foley can be reached on 571-272-0898.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Patricia A. Duffy/
Patricia A. Duffy, Ph.D.
Primary Examiner
Art Unit 1645